PCT

FORM PTO-1390
(REV. 11-94)

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US)

ATTORNEY'S DOCKET NUMBER
8484-029-999

08/913139

INTERNATIONAL APPLICATION NO	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/DE96/00369	March 1, 1996	March 1, 1995

TITLE OF INVENTION
ANTIBODIES ACTIVE AGAINST A FUSION POLYPEPTIDE COMPRISING A HISTIDINE PORTION

APPLICANT(S) FOR DO/EO/US
Hanswalter ZENTGRAF, Claudia TESSMER, Iris VELHAGEN, Susanne Schwinn, Manfred FREY

Applicant herewith submits to the United States Designated/ Elected Office (DO/EO/US) the following items under 35 U.S.C. 371:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.

2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.

3. ☐ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).

4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☒ is transmitted herewith (required only if not transmitted by the international Bureau).
   b. ☐ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)

6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).

7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☒ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureaus.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.

8. ☒ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 37(c)(3)).

9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).

10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.

14. ☒ A substitute specification.

15. ☐ A change of power of attorney and/or address letter.

16. ☒ Other items or information:

One Small Entity Declaration
International Search Report
Preliminary Examination Report

INTERNATIONAL APPLICATION NO PCT/DE96/00369	INTERNATIONAL FILING DATE March 1, 1996

17. ☒ The U.S. National Fee (35 U.S.C. 371(c)(1)) and other fees as follows:

CLAIMS				
(1)FOR	(2)NUMBER FILED	(3)NUMBER EXTRA	(4)RATE	(5)CALCULATIONS
TOTAL CLAIMS	16 -20=	0	X $ 22.00	$ 0.00
INDEPENDENT CLAIMS	3 -3=	0	X $ 80.00	0.00
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $ 260.00	260.00

BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)): **CHECK ONE BOX ONLY** ☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) . . . . . $ 700	
☐ No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) . . . . . $ 770	
☒ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO $1040	1040.00
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2) to (4) . . . . . $ 96	
☐ Filing with EPO or JPO search report . . . . . $ 910	
Surcharge of $130.00 for furnishing the National fee or oath or declaration later than ☐ 20 ☒ 30 mos. from the earliest claimed priority date (37 CFR 1.492(e)).	130.00
TOTAL OF ABOVE CALCULATIONS =	1,430.00
Reduction by 1/2 for filing by small entity, if applicable. Affidavit must be filed also. (Note 37 CFR 1.9, 1.27, 1.28). -	715.00
SUBTOTAL =	715.00
Processing fee of $130.00 for furnishing the English Translation later than ☐ 20 ☐ 30 mos. from the earliest claimed priority date (37 CFR 1.492(f)). +	0.00
TOTAL FEES ENCLOSED $	715.00

a. ☐ A check in the amount of $_____ to cover the above fees is enclosed.

b. ☒ Please charge Deposit Account No. 16-1150 in the amount of $ 715.00 to cover the above fees. A copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 16-1150. A copy of this sheet is enclosed.

18. ☒ Other instructions

Please include the changes to the claims from the Preliminary Amendment before calculating the fee.

19. ☒ All correspondence for this application should be mailed to

PENNIE & EDMONDS LLP
1155 AVENUE OF THE AMERICAS
NEW YORK, NEW YORK 10036-2711

20. ☒ All telephone inquiries should be made to (212) 790-2803

Jon R. Stark	Jon P. Stark	30,111	2 SEPT 97
NAME	SIGNATURE	REGISTRATION NUMBER	DATE

Express Mail No.: EM 202 007 554 US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: ZENTGRAF *et al.*

Serial No.: UNASSIGNED

Group Art Unit: UNASSIGNED

Filed: HEREWITH

Examiner: UNASSIGNED

For: ANTIBODIES ACTIVE AGAINST A FUSION POLYPEPTIDE COMPRISING A HISTIDINE PORTION

Attorney Docket No.: 8484-029-999

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In accordance with Rule 115 of the Rules of Practice, 37 C.F.R. § 1.115, please consider and enter the following amendments and remarks.

IN THE CLAIMS:

Please amend the Claims as follows:

1. (amended) An antibody against a fusion polypeptide comprising a histidine portion, wherein [the] said antibody is directed against [the] said histidine portion, and [the latter] wherein said histidine portion comprises 6-18 histidine residues.

2. (amended) The antibody [according to] of claim 1, [characterized in that it] wherein said antibody is a polyclonal antibody.

3. (amended) The antibody [according to] of claim 1, [characterized in that it] wherein said antibody is a monoclonal antibody.

4. (amended) The antibody [according to] of claim 3, [characterized in that it] wherein said antibody is deposited under ACC 2207 with DSM (German-type culture collection for microorganisms).

5. (amended) A process for the preparation of [an] the polyclonal antibody [according to any one] of [claims 1-4] claim 2, [characterized in that] comprising:

(a) immunizing an animal [is immunized] with a histidine fusion polypeptide; and

[(a)] (b) collecting said polyclonal [antibodies] antibody [are obtained] from the serum of [the] said animal[, or

(b) monoclonal antibodies are obtained after the fusion of animal's spleen cells with myeloma cells].

6. (amended) The process [according to] of claim 5, [characterized in that] wherein a mixture of different histidine fusion polypeptides is used for immunization.

7. (amended) [Use of an antibody according to any one of claims 1 to 4 in a detection] A method for detecting a fusion polypeptide [comprising] having a histidine portion, comprising:

(a) incubating said polypeptide with the antibody of Claim 1, 2, 3, or 4; and

(b) detecting the antibody in a detection reaction.

8. (amended) [Use according to] The method of claim 7, wherein the detection [method] reaction is [a] selected from the group consisting of Western blot, [an] ELISA, [an] immunofluorescence, [or] and immunopreciptation.

Please add the following new Claims 9 and 10:

9. (new) A process for the preparation of the monoclonal antibody of claim 3, comprising:

(a) immunizing an animal with a histidine fusion polypeptide;

(b) fusing the animal's spleen cells with myeloma cells to generate hybridoma cells; and

(c) obtaining said monoclonal antibody form said hybridoma cells.

10. (new) The process of claim 9, wherein a mixture of different histidine fusion polypeptides is used for immunization.

REMARKS

The above amendments are made to comply with the formal requirements set forth in 37 C.F.R. §1.75. They do not introduce new matter, and they are fully supported by the specification of the subject Application and the Claims as originally filed.

Applicants respectfully request that the above-made amendments be made of record in the file history of the instant application.

Respectfully submitted,

Date 2 SEP 97

Jon R. Stark 30,111

Jon R. Stark (Reg. No.)

PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, New York 10036-2711
(212) 790-9090

Enclosure

Antibodies active against a fusion polypeptide comprising a histidine portion

The present invention relates to antibodies which are active against a fusion polypeptide comprising a histidine portion, a process for the preparation thereof and their use.

It is known to express a polypeptide in the form of a histidine fusion polypeptide. In such a polypeptide, a histidine portion of e.g. 6-18 successive histidine residues is fused to the C or N terminus of the polypeptide. Hence it is possible to isolate the histidine fusion polypeptide by means of a nickel-chelate chromatographic column from the supernatant or cell lysate of the cell expressing it.

However, the above column is expensive. Furthermore, its use costs a lot of time. Therefore, it is not suited for the rapid detection of the expression of a histidine fusion polypeptide. But such a detection is necessary, particularly when it shall be used for screening many cells.

Thus, it is the object of the present invention to provide means by which the expression of a histidine fusion polypeptide can be detected rapidly.

According to the invention this is achieved by an antibody which is directed against a fusion polypeptide comprising a histidine portion.

Such an antibody may be a polyclonal or monoclonal antibody, a monoclonal antibody being preferred. The antibody may be obtained from any animal or human being, rabbits being preferred for a polyclonal antibody and mice being preferred for a monoclonal antibody.

In addition, the antibody may be synthetic, portions which are not necessary for the above-mentioned identification

optionally lacking fully or partially therefrom and these portions being replaced by others which give the antibody further favorable properties, respectively.

The expression "fusion polypeptide comprising a histidine portion" comprises a polypeptide (peptide) of any kind and length which has a histidine portion. Such a polypeptide may be expressed by any cells, e.g. bacteria, yeasts, cells of insects, plants and animals, as well as organisms, e.g. transgenic animals. An above histidine portion may comprise e.g. 6-18, preferably 6, successive histidine residues and be fused to the N and/or C terminus of the polypeptide.

A preferred antibody of the present invention, namely a monoclonal mouse antibody having the above identification, was deposited under No. ACC 2207 with the DSM [German-type collection of microorganisms] on February 15, 1995.

Antibodies according to the invention can be prepared according to conventional methods. If polyclonal antibodies and monoclonal antibodies, respectively, are to be prepared, it will be favorable to immunize animals, particularly rabbits for the former antibodies and mice for the latter antibodies, with an above histidine fusion polypeptide e.g. His p53 (cf. German patent application P 42 32 823.3) or His hdm2 (cf. German patent application P 43 39 553.3), preferably a mixture thereof. The animals can be further boostered with the same histidine fusion polypeptide or polypeptides. Other histidine fusion polypeptides or a combination of these and the preceding histidine fusion polypeptide or polypeptides may also be used for boostering. The polyclonal antibodies may then be obtained from the serum of the animals. Spleen cells of the animals are fused with myeloma cells for the monoclonal antibodies.

For the preparation of synthetic antibodies, e.g. the above-obtained monoclonal antibodies may be used as a basis. For this purpose, it is the obvious thing to analyze

the antigen-binding region of the monoclonal antibodies and identify the portions which are necessary and not necessary for the above identification. The necessary portions may then be modified and the non-necessary portions can be fully or partially eliminated and replaced by portions giving the antibodies further favorable properties, respectively. Also, portions can be modified, eliminated or replaced beyond the binding regions of the antibodies. A person skilled in the art knows that particularly the DNA recombination technology is suitable for the above measures. He is perfectly familiar therewith.

Antibodies according to the invention distinguish themselves in that they recognize any fusion polypeptides comprising a histidine portion. Therefore, the antibodies are suitable for the rapid detection of the expression of such fusion polypeptides. This may be carried out in any detection methods, particularly in a Western blot, an ELISA, an immunoprecipitation or an immunofluorescence. For this purpose, the antibodies according to the invention may be labeled, if appropriate, or used in combination with labeled antibodies directed thereagainst.

The present invention is explained by the below examples.

Example 1: Preparation of monoclonal antibodies

Mice were used for immunization. His hdm2 (amino acid 1-284), His hdm2 (amino acid 58-491) and His p53 (amino acid 66-393) (cf. above) were used as antigens. They were dissolved in a buffer comprising 8 M urea, 100 mM NaH_2PO_4, 10 mM Tris-HCl.

Immunization and booster pattern:

Day 1: 50 µl (= 10 µg) His hdm2 (amino acid 1-284)
50 µl (= 10 µg) His hdm2 (amino acid 58-491)
50 µl PBS (phosphate-buffered saline)
150 µl Freund's adjuvant complete
---
300 µl mix

200 µl of the mix were injected into a mouse

Day 30: 50 µl (= 10 µg) His hdm2 (amino acid 1-284)
50 µl (= 10 µg) His hdm2 (amino acid 58-491)
20 µl PBS
120 µl Freund's adjuvant incomplete
---
240 µl mix

200 µl of the mix were injected into the above mouse.

Day 60: 50 µl (= 10 µg) His hdm2 (amino acid 1-284)
50 µl (= 10 µg) His hdm2 (amino acid 58-491)
85 µl PBS
115 µl Freund's adjuvant incomplete
---
300 µl mix

200 µl of the mix were injected into the above mouse.

Day 90: 50 µl (= 10 µg) His hdm2 (amino acid 1-284)
50 µl (= 10 µg) His hdm2 (amino acid 58-491)
200 µl PBS
---
300 µl mix

200 µl of the mix were injected into the above mouse.

Day 180: 150 µl (= 20 µg) His p53 (amino acid 66-393)
150 µl Freund's adjuvant complete
---
300 µl mix

200 µl of the mix were injected into the above mouse.

Day 230: 75 µl (= 10 µg) His p53 (amino acid 66-393)
25 µl (= 5 µg) His hdm2 (amino acid 1-284)
25 µl (= 5 µg) His hdm2 (amino acid 58-491)
125 µl Freund's adjuvant incomplete
---
250 µl mix

200 µl of the mix were injected into the above mouse.

Day 260: 75 µl (= 10 µg) His p53 (amino acid 66-393)
25 µl (= 5 µg) His hdm2 (amino acid 1-284)
25 µl (= 5 µg) His hdm2 (amino acid 58-491)
125 µl PBS
---
250 µl mix

200 ml of the mix were injected into the above mouse.

The mouse was killed on day 262. Spleen cells were removed therefrom and fused with myeloma cells. Monoclonal antibodies were obtained. One of them was deposited under ACC 2207 with DSM on February 15, 1995.

Example 2: Preparation of polyclonal antibodies

Rabbits were used for immunization. The antigens of Example 1 were employed. The immunization and booster pattern was identical with that of Example 1 up to day 90 inclusive.

Day 92: 5 ml of blood were removed from the rabbit's auricular vein and tested for antibody activity in an ELISA and Western blot, respectively.

Day 93: Following a positive test on day 92, the animals were killed and the antibodies were obtained from the serum.

Example 3: Detection of histidine fusion polypeptides by antibodies according to the invention

(a) Western blot

Histidine fusion polypeptides, namely His hdm2 (amino acid 1-284), His hdm2 (amino acid 58-491) and His p53 (amino acid 66-393) of Example 1, as well as the polypeptides hdm2 (amino acid 1-284), WAF 1 (= wild type-activating factor) and t16 (= cell-regulating protein) as control were subjected to a polyacrylamide gel eletrophoresis. The gel was transferred overnight to a nitrocellulose membrane. It was then incubated with the above antibody ACC 2207 diluted in a ratio of 1:10 and 1:50, respectively, at 37°C for 1 hour. After several wash steps using PBS (0.05 % Tween 20), a purchasable alkaline phosphatase-coupled goat-anti-mouse antibody (dilution according to the manufacturer's indication) was added. A 30-minute incubation at 37°C was followed by several wash steps using PBS and thereafter the alkaline phosphatase detection reaction with alkaline phosphatase including developing solution (36 µM 5'-bromo-4-chloro-3-indolylphosphate, 400 µM nitroblue tetrazolium, 100 mM Tris-HCl, pH 9.5, 100 mM NaCl, 5 mM $MgCl_2$) at room temperature until bands were visible.

It showed that the antibody ACC 2207 according to the invention recognizes specifically histidine fusion polypeptides but not polypeptides without histidine portion.

(b) ELISA

A 96-well plate was provided per well with 100 µl each, which included 20 ng and 8 ng, respectively, of the histidine fusion polypeptides and the controls of (a), respectively. After incubation at 4°C overnight, 3 short wash steps using PBS followed. Thereafter, the free binding sites of the polymeric carrier were blocked by one-hour incubation using 1 % BSA in PBS at 37°C. The antibody ACC 2207 according to the invention which was diluted in a ratio of 1:10 and 1:50, respectively, was incubated on the plate at 37°C for 1 hour. After 8 wash steps using PBS, the peroxidase-coupled goat anti-mouse antibody of (a) was added. A 30-minute incubation at 37°C was followed by 8 wash steps and thereafter the peroxidase detection reaction with developing solution (50 mM sodium acetate, 0.4 mM 3,3',5,5'-tetramethylbenzidine dihydrochloride, 4.4 mM H_2O_2) at room temperature until bands were visible.

It showed that the antibody ACC 2207 according to the invention recognizes specifically histidine fusion polypeptides but not a polypeptide without histidine portion.

#4134

Claims

1. An antibody against a fusion polypeptide comprising a histidine portion, wherein the antibody is directed against the histidine portion and the latter comprises 6-18 histidine residues.

2. The antibody according to claim 1, characterized in that it is polyclonal.

3. The antibody according to claim 1, characterized in that it is monoclonal.

4. The antibody according to claim 3, characterized in that it is deposited under ACC 2207 with DSM [German-type culture collection for microorganisms].

5. A process for the preparation of an antibody according to any one of claims 1 to 4, characterized in that an animal is immunized with a histidine fusion polypeptide and

   (a) polyclonal antibodies are obtained from the serum of the animal, or

   (b) monoclonal antibodies are obtained after the fusion of animal's spleen cells with myeloma cells.

6. The process according to claim 5, characterized in that a mixture of histidine fusion polypeptides is used for immunization.

7. Use of an antibody according to any one of claims 1 to 4 in a detection method for a fusion polypeptide comprising a histidine portion.

8. Use according to claim 7, wherein the detection method is a Western blot, an ELISA, an immunofluorescence or an immunopreciptation.

Abstract of the Disclosure

Antibodies active against a fusion polypeptide comprising a histidine portion

The present invention relates to an antibody active against a fusion polypeptide comprising a histidine portion, a process for the preparation thereof and its use.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: ☒ Application of: ZENTGRAF *et al.*
☐ Patent of:

☐ Application No.:
☐ Patent No.:

Group Art Unit: n/a

☒ Filed: Herewith
☐ Issued:

Examiner: n/a

For: ANTIBODIES ACTIVE AGAINST A FUSION POLYPEPTIDE COMPRISING A HISTIDINE PORTION

Attorney Docket No.: 8484-029-999

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS
[37 CFR 1.9(f) and 1.27(d)] - Nonprofit Organization

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I hereby declare that I am an official empowered to act on behalf of the nonprofit organization identified below:

Name of organization Deutsches Krebsforschungszentrum Stiftung Des Öffentlichen Rechts
Address of organization Im Neuenheimer Feld 280, D-69120 Heidelberg GERMANY

Type of organization

☐ University or other institution of higher education
☐ Tax exempt under Internal Revenue Service Code (26 USC 501(a) and 501(c)(3))
☐ Nonprofit scientific or educational under statute of state of the United States of America
(Name of state _____)
(Citation of statute _____)
☒ Would qualify as tax exempt under Internal Revenue Service Code (26 USC 501(a) and 501(c)(3)) if located in the United States of America.
☐ Would qualify as nonprofit scientific or educational under statute of state of the United States of America if located in the United States of America
(Name of state _____)
(Citation of statute _____)

I hereby declare that the nonprofit organization identified above qualifies as a nonprofit organization as defined in 37 CFR 1.9(e) for purposes of paying reduced fees under section 41(a) and (b) of Title 35, United States Code with regard to the invention entitled ANTIBODIES ACTIVE AGAINST A FUSION POLYPEPTIDE COMPRISING A HISTIDINE PORTION by inventor(s) ZENTGRAF, Hanswalter; TESSMER, Claudia; VELHAGEN, Iris; SCHWINN, Susanne; FREY, Manfred described in

☒ the specification filed herewith
☐ application no. filed
☐ patent no. issued

I hereby declare that rights under contract or law have been conveyed to and remain with the nonprofit organization identified above and/or there is an obligation under contract or law by the inventor(s) to convey rights to the nonprofit organization identified above with regard to the invention.

If the rights held by the nonprofit organization are not exclusive, each individual, concern or organization having rights to the invention is listed below* and no rights to the invention are held by any person, other than the inventor, who could not qualify as an independent inventor under 37 CFR 1.9(c) or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e).

FULL NAME____
ADDRESS____

☐ INDIVIDUAL ☐ SMALL BUSINESS CONCERN ☐ NONPROFIT ORGANIZATION

FULL NAME____
ADDRESS____

☐ INDIVIDUAL ☐ SMALL BUSINESS CONCERN ☐ NONPROFIT ORGANIZATION

FULL NAME____
ADDRESS____

☐ INDIVIDUAL ☐ SMALL BUSINESS CONCERN ☐ NONPROFIT ORGANIZATION

FULL NAME____
ADDRESS____

☐ INDIVIDUAL ☐ SMALL BUSINESS CONCERN ☐ NONPROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. [37 CFR 1.28 (b)]

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, and patent issuing thereon, or any patent to which this verified statement is directed.

Send correspondence to: PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, N.Y. 10036-2711

Direct Telephone calls to:
PENNIE & EDMONDS LLP
(212) 790-9090

Name of person signing: Prof.Dr.med.Dr.h.c.mult.H.zur Hausen Dr.rer.pol. J. Puchta

Title of person other than owner: Chairman a.Scient. Member of Board / Adm. Member of the Managememt

Address of person signing: Eichenweg a 69483 Waldmichelbach / Eichenstr. 12a 69 198 Schriesheim

Signature: _____ Date: Oct. 6, 1997

*NOTE: Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below at 201 et seq. underneath my name.

I believe I am the original, first and sole inventor if only one name is listed at 201 below, or an original, first and joint inventor if plural names are listed at 201 et seq. below, of the subject matter which is claimed and for which a patent is sought on the invention entitled

ANTIBODIES ACTIVE AGAINST A FUSION POLYPEPTIDE COMPRISING A HISTIDINE PORTION

and for which a patent application:
☐ is attached hereto and includes amendment(s) filed on _____ *(if applicable)*
☐ was filed in the United States on _____ as Application No. _____ *(for declaration not accompanying application)*
with amendment(s) filed on _____ *(if applicable)*
☒ was filed as PCT international Application No. PCT/DE96/00369 on March 1, 1996 and was amended under PCT Article 19 on _____ *(if applicable)*

I hereby state that I have reviewed and understand the contents of the above identified application, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

EARLIEST FOREIGN APPLICATION(S), IF ANY, FILED PRIOR TO THE FILING DATE OF THE APPLICATION			
APPLICATION NUMBER	COUNTRY	DATE OF FILING (day, month, year)	PRIORITY CLAIMED
195 07 166.2	Germany	1 MAR 1995	YES ☒ NO ☐
			YES ☐ NO ☐

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below.

APPLICATION NUMBER	FILING DATE

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

APPLICATION SERIAL NO.	FILING DATE	STATUS		
		PATENTED	PENDING	ABANDONED

POWER OF ATTORNEY: As a named inventor, I hereby appoint S. Leslie Misrock (Reg. No. 18872), Harry C. Jones, III (Reg. No. 20280), Berj A. Terzian (Reg. No. 20060), Gerald J. Flintoft (Reg. No. 20823), David Weild, III (Reg. No. 21094), Jonathan A. Marshall (Reg. No. 24614), Barry D. Rein (Reg. No. 22411), Stanton T. Lawrence, III (Reg. No. 25736), Isaac Jarkovsky (Reg. No. 22713), Joseph V. Colaianni (Reg. No. 20019), Charles E. McKenney (Reg. No. 22795), Philip T. Shannon (Reg. No. 24278), Francis E. Morris (Reg. No. 24615), Charles E. Miller (Reg. No. 24576), Gidon D. Stern (Reg. No. 27469), John J. Lauter, Jr. (Reg. No. 27814), Brian M. Poissant (Reg. No. 28462), Brian D. Coggio (Reg. No. 27624), Rory J. Radding (Reg. No. 28749), Stephen J. Harbulak (Reg. No. 29166), Donald J. Goodell (Reg. No. 19766), James N. Palik (Reg. No. 25510), Thomas E. Friebel (Reg. No. 29258), Laura A. Coruzzi (Reg. No. 30742), Jennifer Gordon (Reg. No. 30753), Jon R. Stark (Reg. No. 30111), Allan A. Fanucci (Reg. No. 30256), Geraldine F. Baldwin (Reg. No. 31232), Victor N. Balancia (Reg. No. 31231), Samuel B. Abrams (Reg. No. 30605), Steven I. Wallach (Reg. No. 35402), Marcia H. Sundeen (Reg. No. 30893), Paul J. Zegger (Reg. No. 33821), Edmond R. Bannon (Reg. No. 32110), Bruce J. Barker (Reg. No. 33291), Adriane M. Antler (Reg. No. 32605), Ann L. Gisolfi (Reg. No. 31956), Mark A. Farley (Reg. No. 33170), and James G. Markey (Reg. No. 31636), all of Pennie & Edmonds LLP, whose addresses are 1155 Avenue of the Americas, New York, New York 10036, 1667 K Street N.W., Washington, DC 20006 and 3300 Hillview Avenue, Palo Alto, CA 94304, and each of them, my attorneys, to prosecute this application, and to transact all business in the Patent and Trademark Office connected therewith.

SEND CORRESPONDENCE TO: PENNIE & EDMONDS LLP
1155 AVENUE OF THE AMERICAS
NEW YORK, N.Y. 10036-2711

DIRECT TELEPHONE CALLS TO:
PENNIE & EDMONDS LLP DOCKETING
(212) 790-2803

201	FULL NAME OF INVENTOR	LAST NAME: ZENTGRAF	FIRST NAME: Hanswalter	MIDDLE NAME:	
	RESIDENCE & CITIZENSHIP	CITY: Heidelberg	STATE OR FOREIGN COUNTRY: Germany	COUNTRY OF CITIZENSHIP: Germany	
	POST OFFICE ADDRESS	STREET: Bluntschlistraße 6	CITY: Heidelberg	STATE OR COUNTRY: D-	ZIP CODE: 69115
202	FULL NAME OF INVENTOR	LAST NAME: TESSMER	FIRST NAME: Claudia	MIDDLE NAME:	
	RESIDENCE & CITIZENSHIP	CITY: Schwarzach	STATE OR FOREIGN COUNTRY: Germany	COUNTRY OF CITIZENSHIP: Germany	
	POST OFFICE ADDRESS	STREET: Höhenstraße 23	CITY: Schwarzach	STATE OR COUNTRY: D-	ZIP CODE: 74869
203	FULL NAME OF INVENTOR	LAST NAME: VELHAGEN	FIRST NAME: Iris	MIDDLE NAME:	
	RESIDENCE & CITIZENSHIP	CITY: Schwetzingen	STATE OR FOREIGN COUNTRY: Germany	COUNTRY OF CITIZENSHIP: Germany	
	POST OFFICE ADDRESS	STREET: Goestraße 14	CITY: Schwetzingen	STATE OR COUNTRY: D-	ZIP CODE: 68723
204	FULL NAME OF INVENTOR	LAST NAME: SCHWINN	FIRST NAME: Susanne	MIDDLE NAME:	
	RESIDENCE & CITIZENSHIP	CITY: Hockenheim	STATE OR FOREIGN COUNTRY: Germany	COUNTRY OF CITIZENSHIP: Germany	
	POST OFFICE ADDRESS	STREET: Robert-Bosch-Straße 14	CITY: Hockenheim	STATE OR COUNTRY: D-	ZIP CODE: 68766
205	FULL NAME OF INVENTOR	LAST NAME: FREY	FIRST NAME: Manfred	MIDDLE NAME:	
	RESIDENCE & CITIZENSHIP	CITY: Mannheim	STATE OR FOREIGN COUNTRY: Germany	COUNTRY OF CITIZENSHIP: Germany	
	POST OFFICE ADDRESS	STREET: Lessingstraße 12	CITY: Mannheim	STATE OR COUNTRY: D-	ZIP CODE: 68259
206	FULL NAME OF INVENTOR	LAST NAME:	FIRST NAME:	MIDDLE NAME:	
	RESIDENCE & CITIZENSHIP	CITY:	STATE OR FOREIGN COUNTRY:	COUNTRY OF CITIZENSHIP:	
	POST OFFICE ADDRESS	STREET:	CITY:	STATE OR COUNTRY:	ZIP CODE:

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

SIGNATURE OF INVENTOR 201 - ZENTGRAF, Hanswalter	SIGNATURE OF INVENTOR 202 - TESSMER, Claudia	SIGNATURE OF INVENTOR 203 - VELHAGEN, Iris
DATE: 16.12.1997	DATE: 15.12.97	DATE: 16.12.1997
SIGNATURE OF INVENTOR 204 - SCHWINN, Susanne	SIGNATURE OF INVENTOR 205 - FREY, Manfred	SIGNATURE OF INVENTOR 206
DATE: 16.12.1997	DATE: 16.12.1997	DATE:

United States Patent & Trademark Office

Office of Initial Patent Examination -- Scanning Division

Application deficiencies found during scanning:

1. Application papers are not suitable for scanning and are not in compliance with 37 CFR 1.52 because:
   - ☐ All sheets must be the same size and either A4 (21 cm x 29.7 cm) or 8-1/2"x 11". Pages _____ do not meet these requirements.
   - ☐ Papers are not flexible, strong, smooth, non-shiny, durable, and white.
   - ☐ Papers are not typewritten or mechanically printed in permanent ink on one side.
   - ☐ Papers contain improper margins. Each sheet must have a left margin of at least 2.5 cm (1") and top, bottom and right margins of at least 2.0 cm (3/4").
   - ☐ Papers contain hand lettering.

2. Drawings are not in compliance and were not scanned because:
   - ☐ The drawings or copy of drawings are not suitable for electronic reproduction.
   - ☐ All drawings sheets are not the same size. Pages must be either A4 (21 cm x 29.7 cm) or 8-1/2" x 11".
   - ☐ Each sheet must include a top and left margin of at least 2.5 cm (1"), a right margin of at least 1.5 cm (9/16") and a bottom margin of at least 1.0 cm (3/8").

3. Page(s)_____ are not of sufficient clarity, contrast and quality for electronic reproduction.

4. Page(s)_____ are missing.

5. OTHER: NO Drawings